

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 14 February 2001 (14.02.01)	
<b>International application No.</b> PCT/EP00/05321	<b>Applicant's or agent's file reference</b> SCB562PCT
<b>International filing date (day/month/year)</b> 08 June 2000 (08.06.00)	<b>Priority date (day/month/year)</b> 14 June 1999 (14.06.99)
<b>Applicant</b> VILLA, Roberto et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 22 December 2000 (22.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	<b>Authorized officer</b>  Claudio Borton  Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>SCB562PCT</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/EP 00/ 05321</b>	International filing date (day/month/year) <b>08/06/2000</b>	(Earliest) Priority Date (day/month/year) <b>14/06/1999</b>
Applicant  <b>CIP-NINETY TWO-92 S.A.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05321

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K9/20 A61K31/606

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 245 492 <sup>✓</sup> A (ZAMBON SPA) 8 January 1992 (1992-01-08) page 1, line 4 - line 7 page 2, line 11 - line 24 page 6, line 23 -page 8, last line page 10, line 2 page 12, line 13 - line 26; claims; examples 1,16	1,2,4-10
A	WO 98 26767 <sup>✓</sup> A (BUSETTI CESARE ;CRIMELLA TIZIANO (IT); OLGIATI VINCENZO (IT); POLI) 25 June 1998 (1998-06-25) page 3, line 16 -page 4, line 15 page 5, line 12 -page 7, line 19 page 8, line 23 -page 9, line 22; claims; examples 1,2	1-10
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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Marttin, E

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International Application No

PCT/EP 00/05321

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 851 555 A (PRIOR DAVID V ET AL) 22 December 1998 (1998-12-22) column 2, line 34 - line 36 column 2, line 64 -column 3, line 21 column 4, line 10 - line 18; claims 1-12; example 1	1-11
A	US 5 593 690 A (AKIYAMA YOHKO ET AL) 14 January 1997 (1997-01-14) column 1, line 34 -column 2, line 34; claims 1-4 column 3, line 46 -column 4, line 22; examples 23-25	1-11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2245492	A	08-01-1992	IT 1244867 B	12-09-1994
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			JP 2893191 B	17-05-1999
			KR 148002 B	17-08-1998
			NZ 231281 A	29-01-1991
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(21) International Application Number: PCT/EP00/05321

(74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): VILLA, Roberto [IT/PA]; Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA). PEDRANI, Massimo [IT/PA]; Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA). AJANI, Mauro [IT/PA]; Edificio Vallario, Piso 6°, Calle 52 Y Ecuira Mendez, Panama City (PA). FOSSATI, Lorenzo [IT/PA]; Edificio

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(54) Title: MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising: a) an inner lipophilic matrix consisting of substances with melting point below 90 °C in which the active ingredient is at least partly inglobated; b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; c) optionally other excipients.

WO 00/76481 A1

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MESALAZINE      CONTROLLED      RELEASE      ORAL      PHARMACEUTICAL  
COMPOSITIONS

The present invention relates to controlled release oral pharmaceutical compositions containing as active ingredient 5-amino salicylic acid, also named mesalazine.

BACKGROUND OF THE INVENTION

5      Mesalazine is used in the treatment of Chron's disease and ulcerative colitis thanks to its antiinflammatory activity on the intestinal mucuses. Controlled-release formulations of mesalazine are disclosed in WO 95/16451, EP 0 453 001, EP 0 377 477.

10      The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1.    The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the  
15    penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2.    The use of hydrophilic matrices, in which the main component of the matrix structure opposes high  
20    resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3.    The use of bioerodible matrices, which are capable of  
25    being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

30    Inert matrices, for example, generally entail non-linear, but esponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a

certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533,, (1998) which improves the application through an annealing technique of the inert

polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of mesalazine.

When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient.

#### DISCLOSURE OF THE INVENTION

The invention provides controlled release oral

pharmaceutical compositions containing 5-amino-salicylic acid as the active ingredient, comprising:

- a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partially inglobated;
- b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;
- c) optionally other excipients.

#### DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be obtained with a method comprising the following steps:

- a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.

After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

- b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellaable excipients.

This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40

to 90°C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%.

The inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which pass from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrans, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

The lipophilic matrix granules containing the active ingredient are mixed with hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the

hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitables.

The compression of the mixture of lipophilic matrix, hydrogel-forming compounds and, optionally, active ingredient non inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix.

The tablets, capsules and/or minitables obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of for example polymers of methacrylic acids (Eudragit<sup>(R)</sup>) or cellulose derivatives, such as cellulose acetophthalate.

The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses.

In terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the

dissolution profile of the active ingredient.

The following examples illustrate the invention in greater detail.

Example 1

5        770 g of 5-aminosalicylic acid are added in a kneader with 20 g of carnauba wax and 50 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold.

10       The inert matrix granules are loaded into a mixer in which 30 g of Carbopol 971P<sup>(R)</sup> and 65 g of hydroxypropyl methylcellulose are sequentially added.

15       After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 649 mg/tablet or 510 mg/tablet to obtain 500 and 400 mg dosages, respectively.

20       The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

25       The dissolution profile of these tablets shows the release of an active ingredient amount lower than 30% within the first hour of permanence in simulated enteric juice, an amount lower than 60% at the fourth hour and an amount lower than 90% at the eighth hour, thus proving that the double matrix effectively controls dissolution.

Example 2

30       1000 g of 5-aminosalicylic acid are added in a kneader with 10 g of carnauba wax and 20 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold or directly granulated in a high rate mixer.

The resulting granules are loaded into a mixer in which



80 g of hydroxypropyl methylcellulose and 12 g of sodium starch glycolate are sequentially added. After a first mixing step, 11 g of silica colloidal and 11 g of magnesium stearate are added. The final mixture is homogenized, then  
5 tabletted to a unitary weight of 1144 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag  
10 time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 55% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

15 Example 3

850 g of 5-aminosalicylic acid are added in granulator/kneader with 9 g of beeswax and 22 g of palmitic acid with heating, until homogeneous dispersion; then worked to a granulate in a high shear granulating device. The  
20 resulting granules are then loaded into a mixer which is added in succession with 45.5 g of hydroxypropyl methylcellulose, 45.5 g of microcrystalline cellulose, 20 g of sodium starch glycolate, 22 g of colloidal silica and 22 g of magnesium stearate. After homogenization, the final  
25 mixture is tabletted to a unitary weight of 975 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or acetophthalate of cellulose and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag  
30 time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 4

1100 g of 5-aminosalicylic acid are added in granulator/kneader with 10 g of wax carnauba and 20 g of stearic acid.

5 10 g of polyacrylamide, 39.5 of microcrystalline cellulose and 22 g of colloidal silica are separately loaded into the homogenizer/granulator to obtain a homogeneous solid mixture, which is placed in the mixer where the active ingredient has been granulated and homogenized. 49.5 g of  
10 hydroxypropyl methylcellulose and 12 g of sodium alginate are thoroughly mixed, then added with 5 g of calcium carbonate, 34.5 g of microcrystalline cellulose and 11 g of magnesium stearate. The mixture is homogenized, then  
15 tabletted to a final unitary weight of 1194 mg/tablet. The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the  
20 intestine provides the release of no more than 35% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 5

25 1200 g of 5-aminosalicylic acid are added in mixer with 10 g of carnauba wax and 20 g of stearic acid, with heating until homogeneous dispersion, then cold extruded into small granules or directly granulated in the high rate mixer.

The resulting granules are loaded into a mixer, then 70  
30 g of hydroxypropyl methylcellulose and 20 g of sodium starch glycolate are sequentially added.

After a first mixing step, 80 g of sodium carbonate and 5 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to unitary weight of 1375

mg/tablet.

The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

5       The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight  
10       hours.

CLAIMS

1 Controlled-release oral pharmaceutical compositions  
containing as active ingredient 5-amino-salicylic acid,  
5 comprising:

- a) an inner lipophilic matrix consisting of substances  
with melting point below 90°C in which the active  
ingredient is at least partly inglobated;
- b) an outer hydrophilic matrix in which the lipophilic  
10 matrix is dispersed;
- c) optionally other excipients.

2. Compositions as claimed in claim 1, wherein the  
lipophilic matrix consists of compounds selected from  
unsaturated and/or hydrogenated fatty acids, salts, esters  
15 or amides thereof, fatty acid mono-, di- or triglycerids,  
waxes, ceramides, cholesterol derivatives.

3. Compositions as claimed in claim 1 or 2, wherein 5-  
aminosalicylic acid is inglobated in the molten lipophilic  
matrix by kneading, extrusion and/or granulation.

20 4. Compositions as claimed in any one of the above claims,  
wherein the hydrophilic matrix consists of hydrogel-forming  
compounds.

5. Compositions as claimed in claim 4 wherein the  
hydrophilic matrix consists of compounds selected from  
25 polymers or copolymers of acrylic or methacrylic acid,  
alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl  
celluloses, polysaccharides, dextrans, pectins, starches and  
derivatives, alginic acid, natural or synthetic gums.

6. Compositions as claimed in any one of the above claims,  
30 comprising a gastro-resistant outer coating.

7. Compositions as claimed in claim 6, wherein the gastro-  
resistant coating consists of methacrylic acid polymers or  
cellulose derivatives.

8. Compositions as claimed in any one of the above claims,

in the form of tablets, capsules, minitabets, wherein the active ingredient is completely contained inside the lipophilic matrix.

9. Compositions as claimed in any one of claims 1 to 7, in the form of tablets, capsules, minitabets, wherein the active ingredient is dispersed both in the hydrophilic matrix and the lipophilic matrix.

10. Compositions as claimed in any one of the above claims, wherein the percentage of the active ingredient on the total composition weight ranges from 80 to 95%

11. A process for the preparation of the compositions of claims 1-10, which comprises:

- a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90°C;
- b) mixing the granules from step a) with the hydrophilic excipients and subsequent tableting or compression.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/05321

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K31/606

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 245 492 A (ZAMBON SPA) 8 January 1992 (1992-01-08) page 1, line 4 - line 7 page 2, line 11 - line 24 page 6, line 23 -page 8, last line page 10, line 2 page 12, line 13 - line 26; claims; examples 1,16	1,2,4-10
A	WO 98 26767 A (BUSETTI CESARE ;CRIMELLA TIZIANO (IT); OLGATI VINCENTO (IT); POLI) 25 June 1998 (1998-06-25) page 3, line 16 -page 4, line 15 page 5, line 12 -page 7, line 19 page 8, line 23 -page 9, line 22; claims; examples 1,2	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"G" document member of the same patent family

Date of the actual completion of the international search

29 September 2000

Date of mailing of the international search report

06/10/2000

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/05321

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 851 555 A (PRIOR DAVID V ET AL)  22 December 1998 (1998-12-22)  column 2, line 34 - line 36  column 2, line 64 -column 3, line 21  column 4, line 10 - line 18; claims 1-12;  example 1</p> <p style="text-align: center;">---</p>	1-11
A	<p>US 5 593 690 A (AKIYAMA YOHKO ET AL)  14 January 1997 (1997-01-14)  column 1, line 34 -column 2, line 34;  claims 1-4  column 3, line 46 -column 4, line 22;  examples 23-25</p> <p style="text-align: center;">-----</p>	1-11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

CT/EP 00/05321

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2245492	A	08-01-1992	IT 1244867 B	12-09-1994
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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB562PCT		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) <b>FOR FURTHER ACTION</b>	
International application No. PCT/EP00/05321	International filing date (day/month/year) 08/06/2000	Priority date (day/month/year) 14/06/1999	
International Patent Classification (IPC) or national classification and IPC A61K9/20			
Applicant CIP-NINETY TWO-92 S.A.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input type="checkbox"/> Priority</li><li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input type="checkbox"/> Certain observations on the international application</li></ul>			
Date of submission of the demand  08/06/2000		Date of completion of this report  19.03.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  Hedegaard, A  Telephone No. +49 89 2399 8644 	

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05321

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-10 as originally filed

**Claims, No.:**

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05321

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes: Claims 1-11
	No: Claims
Inventive step (IS)	Yes: Claims 1-11
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-11
	No: Claims

### 2. Citations and explanations **see separate sheet**

**R Section V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The subject-matter of claims 1-10 (compositions) and 11 (process) is novel (Art. 33(2) PCT) since an oral pharmaceutical composition containing as active ingredient 5-amino-salicylic acid, comprising an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly inglobated; and an outer hydrophilic matrix in which the lipophilic matrix is dispersed has not been disclosed in the available prior art documents.

D1 (= GB-A-2 245 492), which represents the closest prior art, discloses (see example 16) an oral pharmaceutical composition made of a core comprising 5-amino-salicylic acid, said core being coated with an inner lipophilic layer and an outer enteric coating. However, there is no disclosure of an outer hydrophilic matrix in which the lipophilic matrix is dispersed.

2. The problem of the present application was to provide controlled release oral pharmaceutical compositions containing 5-amino salicylic acid (mesalazine), wherein a starting burst effect has been avoided.

There was no hint in D1 (alone or in combination with any of the other available prior art documents) that said problem could be solved by the compositions according to present claim 1, said compositions having an inner lipophilic matrix in which the active ingredient is at least partly inglobated; and an outer hydrophilic matrix in which the lipophilic matrix is dispersed. Therefore, the subject-matter of claims 1-11 is considered to involve an inventive step (Art. 33(3) PCT).

## PATENT COOPERATION TREATY

PCT

REC'D 21 MAR 2001

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference SCB562PCT	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/05321	International filing date (day/month/year) 08/06/2000	Priority date (day/month/year) 14/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/20		
Applicant CIP-NINETY TWO-92 S.A.		

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- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  22/12/2000	Date of completion of this report  19.03.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Hedegaard, A  Telephone No. +49 89 2399 8644  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05321

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

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- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/05321

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**Re S ction V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The subject-matter of claims 1-10 (compositions) and 11 (process) is novel (Art. 33(2) PCT) since an oral pharmaceutical composition containing as active ingredient 5-amino-salicylic acid, comprising an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly inglobated; and an outer hydrophilic matrix in which the lipophilic matrix is dispersed has not been disclosed in the available prior art documents.

D1 (= GB-A-2 245 492), which represents the closest prior art, discloses (see example 16) an oral pharmaceutical composition made of a core comprising 5-amino-salicylic acid, said core being coated with an inner lipophilic layer and an outer enteric coating. However, there is no disclosure of an outer hydrophilic matrix in which the lipophilic matrix is dispersed.

2. The problem of the present application was to provide controlled release oral pharmaceutical compositions containing 5-amino salicylic acid (mesalazine), wherein a starting burst effect has been avoided.

There was no hint in D1 (alone or in combination with any of the other available prior art documents) that said problem could be solved by the compositions according to present claim 1, said compositions having an inner lipophilic matrix in which the active ingredient is at least partly inglobated; and an outer hydrophilic matrix in which the lipophilic matrix is dispersed. Therefore, the subject-matter of claims 1-11 is considered to involve an inventive step (Art. 33(3) PCT).